Translation

PCT/JP2003/013123

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C1-A0313P2	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP2003/013123	International filing date (*day/month/year*) 14 October 2003 (14.10.2003)	Priority date (*day/month/year*)

International Patent Classification (IPC) or national classification and IPC
C12N 15/09, C07K 16/18, A61K 39/395, A61P 7/00, 31/12, 35/00, 37/00

Applicant
CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22 April 2005 (22.04.2005)	12 October 2005 (12.10.2005)
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/013123

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box III.1

Claims 20 and 36

Claims 20 and 36 set forth inventions that are related to methods for the treatment of the human body by means of therapy.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box IV.3

The claims of the present invention include:

(1) inventions related to a "bispecific antibody with an activity that substitutes for the ligand function of receptors that include heteromolecules," which are set forth in claims 2 to 19, 21 and 22; and

(2) inventions related to a "bispecific antibody that is capable of recognizing both an enzyme and the substrate of said enzyme," which are set forth in claims 23 to 35, 37 and 38.

Therein, the only feature that is common to these inventions is the feature of being a bispecific antibody (i.e. a dual-specific antibody). However, dual-specific antibodies were well known prior to the filing of the present application, as presented in documents 1 and 2 indicated below; thus, said feature cannot be said to be a special technical feature in the meaning of PCT Rule 13.2. As a result, the inventions in question cannot be considered to be so linked as to form a single general inventive concept, and consequently, the claims of the present application have been found to include two inventions.

Document 1: J. Immunol., Vol. 150, No. 10, pp. 4610 to 4619, 1993

Document 2: J. Immunol. Methods, Vol. 248, No. 1-2, pp. 1 to 6, 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5-19, 21-35, 37, 38	YES
	Claims	1-4	NO
Inventive step (IS)	Claims	23-35, 37, 38	YES
	Claims	1-19, 21, 22	NO
Industrial applicability (IA)	Claims	1-19, 21-35, 37, 38	YES
	Claims		NO

2. Citations and explanations

Document 1: J. Immunol., Vol. 150, No. 10, pages 4610 to 4619, 1993

Document 2: J. Immunol. Methods, Vol. 279, No. 1-2, pages 219 to 232, August 2003

Document 3: J. Immunol. Methods, Vol. 267, No. 2, pages 213 to 226, 2002

Document 4: J. Immunol. Methods, Vol. 248, No. 1-2, pages 1 to 6, 2001

Document 5: J. Immunol. Methods, Vol. 248, No. 1-2, pages 7 to 15, 2001

Document 6: Gene, Vol. 196, No. 1-2, pages 279 to 286, 1997

Claims 1 to 4

The inventions set forth in claims 1 to 4 lack novelty and do not involve an inventive step in the light of document 1 cited in the international search report.

Document 1 indicates that bispecific antibodies capable of bonding to the α chain and the β chain of the human IL-2 receptor were able to synergistically control IL-2 induced T cell proliferation. In addition, document 1 further indicates that IL-2 is one type of cytokine, and that the ligands thereof include both agonists and antagonists.

Claim 1

The invention set forth in claim 1 lacks novelty and does not involve an inventive step in the light of documents 2 to 5 cited in the international search report.

Documents 2 and 3 indicate that bispecific antibodies capable of bonding to two receptors that have different VEGFs (e.g. KDR and Flt-1) were able to control the VEGF-induced migration of leukaemia cells.

Meanwhile, document 4 presents general information pertaining to therapeutic agents against cancer, which comprise bispecific antibodies that are capable of bonding to cancer antigens (e.g. EGF receptor-associated cancer antigens, HER2 antigens or prostate-specific cancer antigens (PSA)), and indicates that recombinant antibodies were obtained by using a phage display library and selecting a scFv that is capable of bonding to a desired antigen.

Furthermore, document 5 presents therapeutic agents against cancer, which comprise bispecific antibodies that are capable of bonding to two types of receptors (e.g. c-Mpl and HER3).

Claims 5 to 19, 21 and 22

The inventions set forth in claims 5 to 19, 21 and 22 do not involve an inventive step in the light of documents 1, 4 and 6 cited in the international search report.

Document 1 indicates that bispecific antibodies capable of bonding to the α chain and the β chain of the human IL-2 receptor were able to synergistically control IL-2 induced T cell proliferation. In addition, document 1 also indicates that in addition to serving as inhibiting factors, it is also possible for the bispecific antibodies to exhibit agonist functions (refer to the final sentence

of the Discussion).

Document 4 indicates that recombinant antibodies were obtained by using a phage display library and selecting a scFv that is capable of bonding to a desired antigen when creating bispecific antibodies.

Document 6 indicates that type-I interferon receptors comprise two sub-units (IFNaR1 and IFNaR2), and presents the bonding mechanism thereof, wherein type-I interferon, which is a ligand, forms an intermediate with IFNaR2 and then said intermediate forms a ternary complex with IFNaR1.

Therefore, it would have been easy for a person skilled in the art to conceive of creating bispecific antibodies which are capable of bonding to the two types of sub-unit within the type-I interferon receptors that are presented in document 6 instead of the two types of sub-unit within the human IL-2 receptors that are presented in document 1 by means of the technique that is presented in document 4, and then selecting the antibodies that exhibit an antagonist function thereamong.

Claims 23 to 35, 37 and 38

The inventions set forth in claims 23 to 35, 37 and 38 are novel and involve an inventive step in relation to the documents that are cited in the international search report.

The documents in question do not present bispecific antibodies that are capable of recognizing both an enzyme and the substrate of said enzyme, and it would not have been easy for a person skilled in the art to conceive of the feature in question.